

## BSACI guidelines for the investigation of suspected anaphylaxis during general anaesthesia

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### Clinical & Experimental Allergy

#### Summary

Investigation of anaphylaxis during general anaesthesia requires an accurate record of events including information on timing of drug administration provided by the anaesthetist, as well as timed acute tryptase measurements. Referrals should be made to a centre with the experience and ability to investigate reactions to a range of drug classes/substances including neuromuscular blocking agents (NMBAs) intravenous (i.v.) anaesthetics, antibiotics, opioid analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), local anaesthetics, colloids, latex and other agents. About a third of cases are due to allergy to NMBAs. Therefore, investigation should be carried out in a dedicated drug allergy clinic to allow seamless investigation of all suspected drug classes as a single day-case. This will often require skin prick tests, intra-dermal testing and/or drug challenge. Investigation must cover the agents administered, but should also include most other commonly used NMBAs and i.v. anaesthetics. The outcome should be to identify the cause and a range of drugs/agents likely to be safe for future use. The allergist is responsible for a detailed report to the referring anaesthetist and to the patient's GP as well as the surgeon/obstetrician. A shorter report should be provided to the patient, adding an allergy alert to the case notes and providing an application form for an alert-bracelet indicating the wording to be inscribed. The MHRA should be notified. Investigation of anaphylaxis during general anaesthesia should be focussed in major allergy centres with a high throughput of cases and with experience and ability as described above. We suggest this focus since there is a distinct lack of validated data for testing, thus requiring experience in interpreting tests and because of the serious consequences of diagnostic error.

**Keywords** allergy, anaphylaxis, anaphylaxis incidence, antibiotics, general anaesthesia, general anaesthetics, latex, local anaesthetic, neuromuscular blocking drugs/agents, patent blue dye, plasma substitute, skin tests

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Cite this as: P. W. Ewan, P. Dugué,  
R. Mirakian, T. A. Dixon, J. N. Harper and  
S. M. Nasser, *Clinical & Experimental  
Allergy*, 2010 (40) 15–31.

#### Executive summary

- This document describes the investigation of suspected anaphylaxis during anaesthesia focussing on the allergist's role.
- Referral should be made to a major allergy centre with expertise in drug allergy and high throughput of anaesthetic anaphylaxis because of the need for experience in interpreting tests and the serious consequences of diagnostic error. The anaesthetist is responsible for referral.
- The centre should be able to investigate all potential causes. This involves a range of drug classes/substances including neuromuscular blocking agents (NMBAs), intravenous (i.v.) anaesthetics, antibiotics, opioid analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), local anaesthetics (LAs), colloids, latex, skin antiseptics and other agents used during general anaesthesia.
- A lead anaesthetist should be identified in each major hospital for clinical governance and notified of each case of anaphylaxis. The responsibility would be to provide initial guidance on blood sampling for serum tryptase and to assist in the process of referral to a specialist centre for further investigation.
- Investigation should be in a dedicated drug allergy clinic so that in most cases a seamless approach to investigation can be undertaken to allow all suspected

drug classes to be considered and investigation completed in one day.

- Before the patient is seen, it is essential to obtain the anaesthetic record, drug charts and anaesthetist's notes as well as results of acute tryptase measurements. This provides a shortlist of likely cause(s) and guides subsequent investigation.
- Serum tryptase is the only helpful blood test required at the time of the reaction to confirm anaphylaxis. Two timed blood samples (5 mL clotted) should be taken: one immediately after resuscitation and one at 1–2 h. If this is missed, a timed sample may be taken up to 6 h, although this may be less helpful. A baseline sample should also be taken at 24 h or later by the investigating allergist.
- Stepwise investigation is necessary and depends on the likely cause, but a suspected IgE-mediated reaction (e.g. NMBAs, i.v. anaesthetics, antibiotics, latex) requires skin testing and in some cases drug challenge.
- For other causes, e.g. a non-IgE-mediated reaction to NSAIDs or opioids, there are no useful skin/blood tests and a clinical diagnosis is reached either by excluding other potential causes or by confirmation with an oral challenge.
- Because of lack of validated data for most drugs, clinical judgment is essential in the interpretation of the investigations and any conclusions reached must be compatible with the clinical history. Hence, guidelines need to be adapted for individual patients.
- When it is clinically likely that an agent given at induction has caused an allergic reaction but the cause has not been identified on the initial visit, the skin tests should be repeated at a later date.
- The aim of the investigation should be to identify the cause of anaphylaxis and to recommend a range of drugs/agents likely to be safe for future use.
- The allergist is responsible for a detailed report to the referring doctor and GP, and a shorter report and provision of 'medical alert' wording to the patient.
- An allergy alert and appropriate coding should be added to the patient's hospital and GP records. This is the responsibility of the investigating allergist, referring anaesthetist and GP after the report has been received.

## Introduction

This guideline focuses on investigation of anaphylaxis during general anaesthesia to determine aetiology. However, it is important for the investigating physician to be aware that some of the clinical features of anaphylaxis may be mimicked by other complications of anaesthesia including difficulty in tracheal intubation, equipment failure or covert haemorrhage. In some instances, adverse reactions can be related to the underlying medical condi-

tion, e.g. septicaemia, or can be due to the expected pharmacological actions of drugs administered, e.g. hypotension. Investigation can be challenging, as the patient is exposed to many co-administered drugs and agents, any of which may be implicated although NMBAs are a major cause. Antibiotic, NSAID and latex sensitivity are included but detailed investigation is described in separate guidelines. There are no reported cases of allergy to inhalational anaesthetics.

This guidance for the investigation of suspected anaphylaxis during general anaesthesia has been prepared by the Standards of Care Committee of the British Society for Allergy and Clinical Immunology (BSACI). The guideline is based on evidence as well as on expert opinion and is for use by specialists practising in drug allergy. Evidence for the recommendations was obtained from electronic literature searches using the primary key words – general anaesthesia, general anaesthetic, neuromuscular blocking drugs/agents, antibiotics, plasma substitute, patent blue dye, latex and local anaesthetic, and combining these search terms with allergy, anaphylaxis or skin tests. Each article was reviewed for suitability for inclusion in the guideline. Where evidence was lacking, consensus on recommendations was reached in consultation with experts in allergy, immunology and anaesthesia. The recommendations in the executive summary were not evidence graded in this guideline; most are based on expert consensus and best-practice because validation of tests to general anaesthesia drugs is not practical as challenge with anaesthetic drugs is not possible. During the development of these guidelines, all BSACI members were included in the consultation process using a web-based system. Their comments and suggestions were considered by the Standards of Care Committee.

## Terminology

Anaphylaxis is an acute severe allergic reaction. The clinical features of anaphylaxis can vary, but typically comprise hypotension and/or respiratory difficulty (laryngeal oedema or asthma) often in association with cutaneous features such as urticaria, erythema or angio-oedema. Other features may also be present [1].

Previously the term anaphylaxis was used only for IgE-mediated reactions. The term anaphylactoid reaction was used for a similar clinical reaction but occurring via a non-IgE-dependent mechanism. This distinction cannot be made unless the aetiology is known and the relevant mechanism is defined. It is of relevance only to identify appropriate tests to determine aetiology and does not help the clinician making the initial diagnosis. A new definition has been proposed by the European Academy for Allergology and Clinical Immunology, whereby all reactions are described as anaphylaxis and sub-divided into allergic or non-allergic anaphylaxis only after diagnostic

testing [2]. This has merit, as the initial diagnosis is determined by the clinician based on clinical presentation, without knowledge of cause or mechanism. Therefore, the term anaphylaxis is used to describe both IgE- and non-IgE-mediated reactions and this terminology is used throughout this document.

### *Incidence*

The UK's Department of Health has set up a 'Yellow Card' system, which collects information on suspected adverse drug reactions. Despite this system, there is considerable under-reporting and the frequency of these reactions is not clearly known. In addition, the figures will depend on whether investigators reported anaphylactic reactions only or adverse reactions of any type. Large epidemiological studies have been reported from Australia and France. In France, there has been an epidemiological study of suspected anaphylactic reactions occurring during anaesthesia since 1984 [3]. The report covering July 1994 to December 1996 [4] included 1648 patients. The incidence of anaphylactic reactions to anaesthetics was 1 in 13 000 while the incidence of anaphylaxis to NMBAs was 1 in 6500. Subsequent reports include the 1999–2000 report (789 patients) [5] and 2001–2002 (712 patients) [6]. In Australia [7, 8], the incidence was reported to be between 1 in 10 000 and 1 in 20 000 anaesthetics in 1993. By extrapolating these data, 175–1000 reactions are estimated in the United Kingdom each year [9]. However, it is likely that the statistics will change with time, for example with changes in usage of anaesthetic agents, with the increased co-administration of other drugs accounting for a larger proportion of cases, e.g. antibiotics and analgesics and with the increase in latex allergy in the last 20 years. This is evident from clinical practice in the United Kingdom and from three French series over a decade, showing a substantial rise of anaphylaxis during anaesthesia, due to antibiotics or latex [5, 6]. An increase above the estimated incidence has also been noted in a study where patients were systematically followed up after adverse reactions during anaesthesia [10]. Therefore, the incidence of anaphylaxis and associated morbidity/mortality during anaesthesia in the United Kingdom remains uncertain but is likely to be higher than currently reported.

### *Risk factors*

Previous anaphylaxis and a severe undiagnosed adverse event during a previous anaesthetic are risk factors [11]. Spina bifida is a risk factor for the development of latex allergy and mastocytosis is a risk factor for anaphylaxis to certain drugs [12].

## **Aetiology**

The causes of adverse reactions during anaesthesia are shown in text box 1.

### *Clinical features of anaphylactic reactions*

In order to investigate adverse reactions during anaesthesia, it is essential to have a good knowledge and understanding of anaphylaxis (reviewed in [13–15]) as well as experience of allergy skin tests to drugs and of challenge tests with a wide range of drugs and substances used during general anaesthesia.

In anaphylaxis, the clinical features are to some extent dependent on the cause and route of administration of allergens. Allergy to a drug given i.v. as a bolus is of rapid onset, usually within minutes of administration and predominantly causes cardiovascular collapse [16]. In contrast, with a rectally administered drug, there is usually a delay of 15–30 min to onset, and urticaria, angio-oedema or asthma is common. Similarly, an i.v. infusion of gelatine usually takes 15–30 min to cause a reaction. In latex rubber allergy, where the allergen is absorbed through the peritoneum, mucosa or skin, a mixed clinical picture is seen, and the onset may be >30 min from first contact. The key features of anaphylaxis to an i.v. induction agent are shown in Table 1. The common initial clinical features seen by the anaesthetist are: loss of pulse, fall in arterial pressure, difficulty in inflating the lungs and flushing [8]. The timing in relation to drug administration is important, and gives a clue to the aetiology (Table 2).

## **Mechanisms**

Anaphylactic reactions are classically mediated by IgE antibodies. Interaction of allergen with specific IgE bound to mast cells (and basophils) leads to cell activation and

### **box 1. Causes of severe adverse events during anaesthesia**

- Exaggerated pharmacological effect, e.g. hypotension during extradural anaesthesia or with propofol; bradycardia and hypotension after opiates
- Anaphylaxis to one of the i.v. NMBAs or anaesthetic drugs
- Adverse reaction to another administered drug  
e.g. drug with pre-medication; antibiotic with induction; analgesic, e.g. NSAID rectally or opiate intra-operatively
- Latex rubber allergy
- Reaction to intravenous infusion, e.g. colloid, blood, plasma
- Allergy to other substance given, e.g. chlorhexidine or a diagnostic dye
- Problem with anaesthetic technique, e.g. intubation
- Autonomic parasympathetic effects, e.g. during laparoscopy, peritoneal traction, arthroscopy, squint surgery, dental surgery
- Blood loss
- Medical (non-allergic) cause, e.g. septicaemia; cardiac; severe asthma, pneumothorax; air embolus
- Malignant hyperthermia

**Table 1.** Anaphylaxis due to intravenous induction agents in general anaesthesia

Clinical features	Frequency (%)
Cardiovascular collapse	88
Bronchospasm	36
Angio-oedema (facial, periorbital, perioral)	24
Angio-oedema (generalized)	7
Other cutaneous features	
Erythema	45
Rash	13
Urticaria	8

Data from Fisher and Baldo [7, 8].

mediator release. Mediators such as histamine cause capillary leakage, mucosal oedema and smooth muscle contraction, resulting in the clinical features observed. In non-IgE-mediated reactions, mast cell or basophil activation and mediator release occur without involvement of IgE antibodies, for example a drug may activate mast cells directly. The features of anaphylactic and anaphylactoid reactions are often clinically indistinguishable. However, differentiating between mechanisms is important when investigating the patient: a negative test for specific IgE does not rule out the investigated drug if the mechanism is not IgE-mediated. Investigation of certain drugs, where the mechanism is unknown, is particularly complex and increases the need for challenge testing.

### Investigation

The Association of Anaesthetists and the BSACI have published guidelines on suspected anaphylactic reactions associated with general anaesthesia [17]. These are aimed primarily at the anaesthetist, whereas the present document focuses on the later investigation of aetiology by the allergist.

#### *Immediate tests by anaesthetist*

Serum tryptase is the only useful blood test during the acute allergic reaction [18, 19]. Serum tryptase is elevated with mast cell activation and is released in both anaphylactic and anaphylactoid reactions. When elevated, serum tryptase is invaluable and indicates that anaphylaxis has occurred, but does not help to identify the specific cause. Serum tryptase peaks quickly within an hour of onset of the reaction, so a 5 mL blood sample (clotted) should be taken at this time point. In some cases of anaphylaxis caused by an injected drug, the serum tryptase level is higher immediately after the onset than at 1 h (unpublished), and therefore two blood samples should be taken: the first immediately after the patient is resuscitated and a second within 2 h. However, the level may still be raised for several hours after the onset of the reaction, and so

blood taken up to 6 h afterwards may still be of value. It is essential to record the time each sample was taken. If required, samples can be stored at 4 °C for 24–48 h in clinical biochemistry and posted first class to an immunology laboratory, either as whole blood or as serum. The assay is widely available through most regional immunology laboratories.

In a study of 789 patients with allergic reactions during anaesthesia, the positive predictive value of tryptase for the diagnosis of anaphylaxis during anaesthesia was 93% and the negative predictive value was 54% [5]. Mast cell tryptase is not always raised in anaphylaxis, and the level may depend on the clinical scenario. For example, with parenteral drug administration or if hypotension is present, serum tryptase is more likely to be raised [20]. Therefore, a normal mast cell tryptase does not exclude anaphylaxis. A baseline tryptase is needed to interpret the results, but can be taken either > 24 h after the reaction when the patient has recovered or when the patient is referred for later investigation [21].

Urinary histamine provides another index of mast cell activation; however, this test is less sensitive and not readily available. A spot urine sample is taken within 4 h of the reaction. In practice, it does not add to the information gained from the serum tryptase and is not recommended.

It was suggested in earlier guidelines [22] that serial measurements of complement levels should be measured, but this is of no value.

#### *Later investigation by allergist*

Patients should be referred to an allergist in a nationally recognized centre, with a high throughput of cases each year and with comprehensive drug testing expertise (not only for NMBAs) including interpretation of skin tests and experience in and facilities for drug challenge. Experience is critical because of lack of data on validation of skin tests and drug challenge, which can result in pseudo-allergic reactions, often requiring single blind provocation [21]. Testing should be focussed in a small number of centres nationally because of the range of drug allergy expertise required and the serious consequences of an incorrect diagnosis. Drug challenges should be performed by appropriately trained personnel (box 2).

#### *General approach and problems*

Many classes of drugs may have to be considered. Therefore, expertise and facilities to test all potential causes should be available in a dedicated drug allergy clinic so that for most patients investigation can be completed as a single day-case (Fig. 2). In some cases, testing is hindered by a lack of knowledge of which tests might be appropriate. For many drugs the mechanism of reaction is not

**Box 2. Roles of anaesthetist and allergist****Role of the anaesthetist (Fig. 1)**

- Detect and identify the reaction as suspected anaphylaxis
- Provide acute treatment of anaphylaxis [23]
- Take timed blood samples for tryptase, immediately after onset (as soon as reasonable after resuscitation) and at 1–2 h
- Notify patient and refer to a nationally recognized allergy centre specializing in drug allergy including anaphylaxis during anaesthesia
- Provide a detailed record of events with timings of all drugs administered in relation to onset
- Lead anaesthetist should be identified in each major hospital for clinical governance and notified of each case of anaphylaxis to ensure that referral takes place
- Add 'Allergy Alert' to patient's hospital records and computer systems once report is received
- Report to MHRA (<http://www.mhra.gov.uk/index.htm>)

**Role of the allergist (Fig. 2)**

- Identify the cause of the reaction
- Identify drugs likely to be safe for future anaesthesia
- Provide a written report to referring consultant, copied to GP and surgeon
- Provide patient with a brief 'to whom it may concern' letter (listing the above)
- Provide patient with an 'Alert' application and the specific wording to be inscribed
- Add Allergy Alert to patient's records and hospital computer systems
- Report to MHRA (<http://www.mhra.gov.uk/index.htm>)

known and there are inadequate data and/or validation of tests. Even where tests are established, interpretation of skin tests can be difficult because of a lack of consensus on the drug concentration to be used for testing or the definition of a positive test. Experience of conducting large numbers of tests is therefore essential.

**History**

The starting point is the history of the reaction. This is provided in the anaesthetic record, drug charts and any additional description or note from the anaesthetist. It is essential to obtain these. In some cases, the hospital notes should be obtained and examined. One should never work from a referral letter only, since drugs and events that the anaesthetist or surgeon might not consider important may not be mentioned. The timing of the reaction in relation to events, e.g. induction, start of surgery, administration of other drugs, i.v. fluids, etc., is essential (Table 2) and should help identify a likely cause. Clarification of which drugs were given before, as opposed to after, the onset of anaphylaxis is often only possible by looking at the anaesthetic chart, and the referring anaesthetist may need to be contacted. It is also important to exclude anaesthetic or surgical problems as the cause; this requires knowledge of the procedure and study of the anaesthetic record.

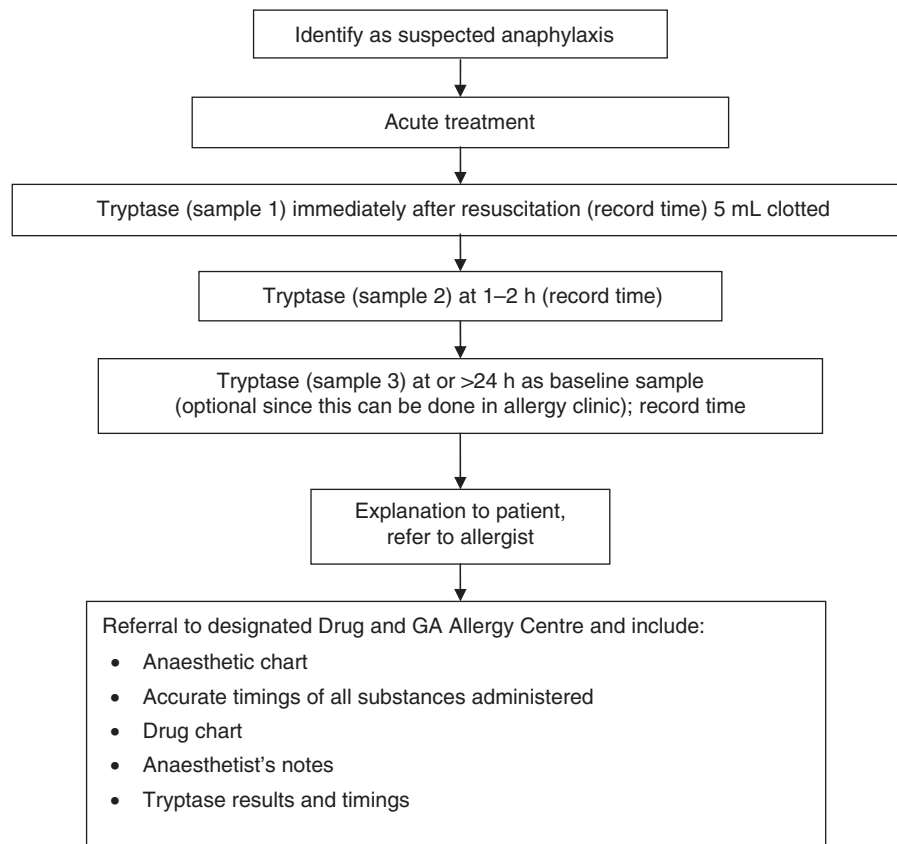


Fig. 1. Anaesthetist's role: immediate action to support investigation of anaphylaxis during anaesthesia.

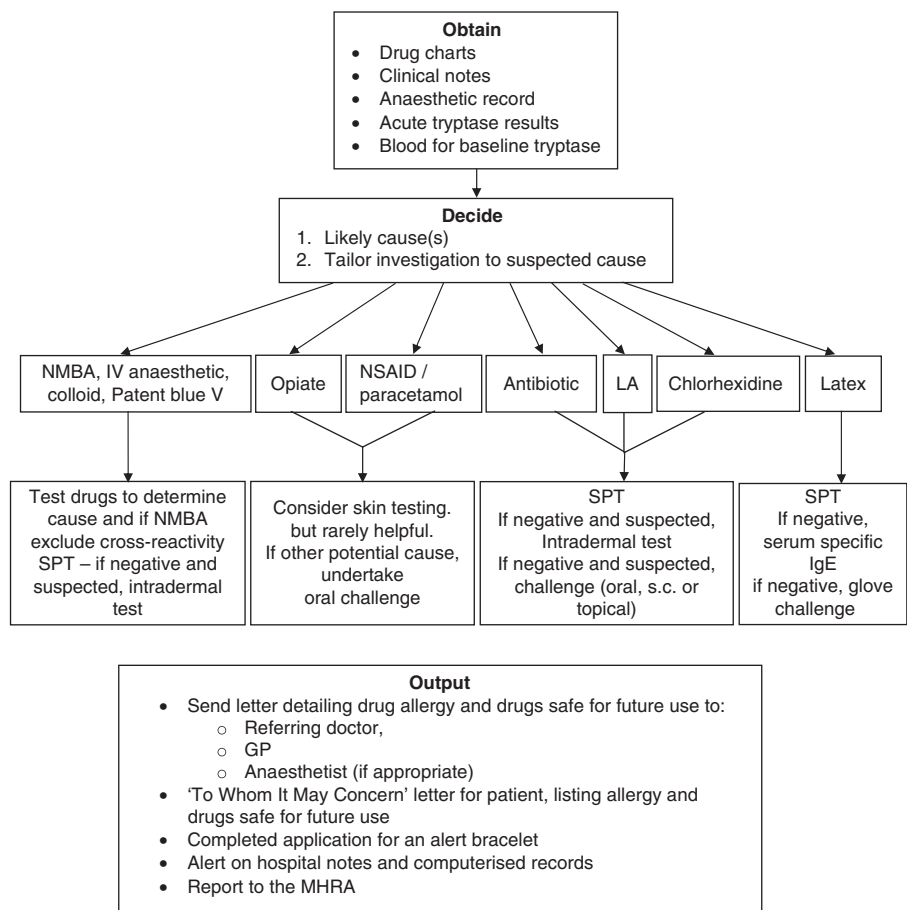


Fig. 2. Allergist's role in the investigation of suspected anaphylaxis during general anaesthesia.

Table 2. Timing of onset of adverse events informs potential aetiology

Within minutes of induction	Intra-operative	Towards end of surgery/recovery
NMBAs	I.v. NSAID/paracetamol	Rectal NSAID
Intravenous anaesthetics	Intravenous opiate	Intravenous opiate
Intravenous opiate	Intravenous antibiotic	Colloid
Intravenous antibiotic with induction	Local anaesthetic	Reversal agents
	Colloid (> 15 min from start of infusion)	Latex rubber allergy
	Latex rubber allergy	
	Dyes/contrast media	
	Chlorhexidine	
	Povidone iodine	
Technical anaesthetic problem	Surgical problem	

A detailed medical history is necessary, e.g. asthma may be the sole cause of a bronchospasm event during general anaesthesia (see text box 1). Centres dealing with large numbers of such patients are familiar with anaesthetic drugs, records and terminology.

Time of onset and clinical features indicate likely causes (Table 2). Anaphylaxis to the i.v. induction agents and antibiotics occurs within minutes of administration, as a large bolus of allergen is given intravascularly. In contrast, in latex allergy, the allergen is absorbed more slowly, e.g. from surgeon's gloves through the peritoneum, mucosa or skin or from rubber equipment, although rubber anaesthetic facemasks have been almost entirely replaced with non-rubber alternatives, and endotracheal tubes and laryngeal masks are latex-free. Onset is therefore slower and occurs intra-operatively, perhaps 30 min from the start of contact with latex, but depends on the sensitivity of the patient and the amount of allergen absorbed. Latex absorption is faster from the vaginal mucosa and peritoneum than through skin. Reactions to gelatine often occur 15–20 min after the start of infusion. Similarly, reactions to chlorhexidine may be delayed – perhaps 10 min after mucosal contact, e.g. bladder instillation and longer after skin painting, although entry of chlorhexidine directly into the circulation, for example during central venous catheter insertion, may result in immediate circulatory collapse. Therefore, if the appropriate documentation is available, it should be

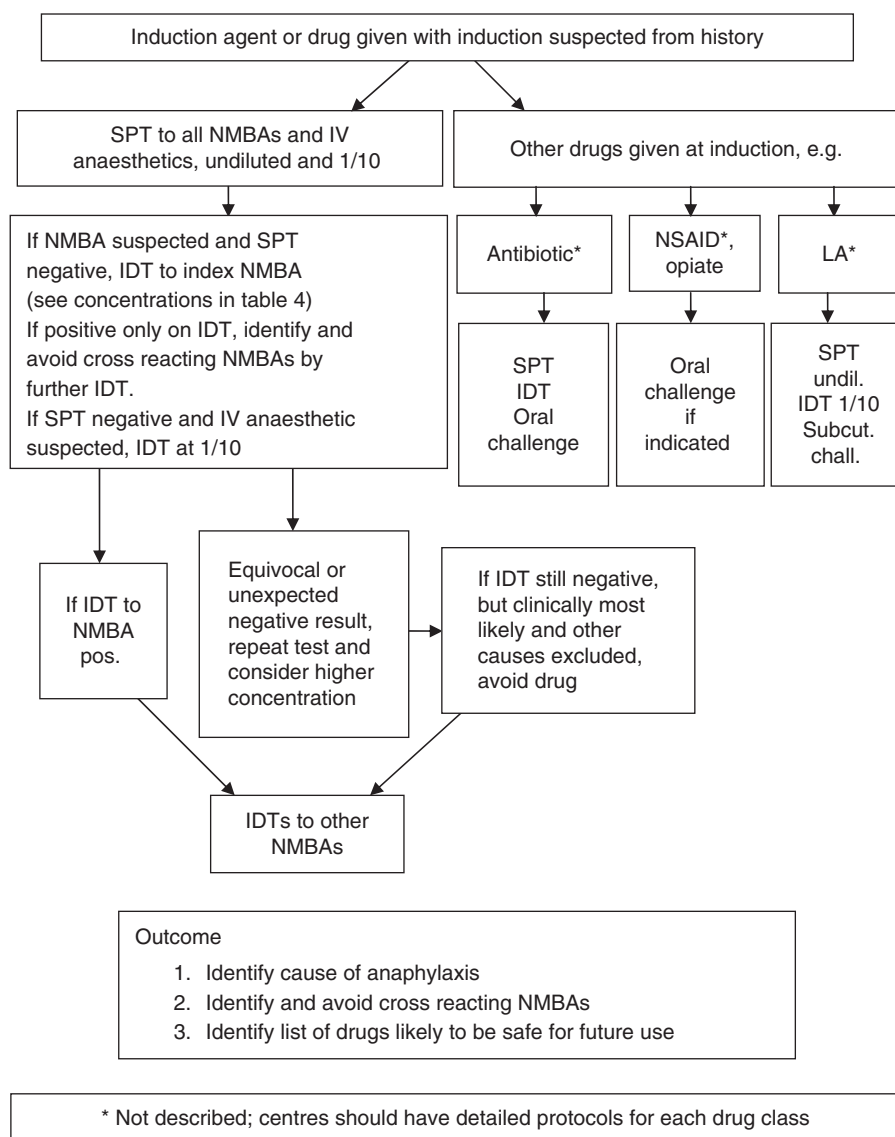


Fig. 3. Testing protocol for allergy to neuromuscular blocking drugs (NMBAs) and intravenous (i.v.) anaesthetics or other drugs given at induction.

possible from the history to identify a short list of likely causes.

The aim should be to obtain the relevant records before the patient is seen as a day-case in a dedicated drug and anaesthetic clinic. Investigation will depend on the cause suspected from the history (text box 1, Table 2 and Fig. 2). This should allow all drug classes to be considered with a step-wise approach so that in most patients investigation can be completed in a single visit (Figs 2 and 3). The centre should stock the wide range of drugs required for testing and have protocols for testing each of the drug classes and dilutions of specific drugs. Specialist allergy nurse support is required.

### Causes of anaphylaxis

In earlier series, up to 70% of anaphylaxis was caused by NMBAs [3, 7, 8]. However, although NMBAs remain the

most common cause, clinical impression from major centres in the United Kingdom and a study of three series from France over a decade suggest that other causes are increasingly prominent. NMBAs now account for just over one-third of all cases and just over half of all cases of anaphylaxis, with an increase in anaphylaxis caused by latex and antibiotics (Table 3) [3, 5, 6]. In contrast to the NMBAs, anaphylaxis to i.v. anaesthetics is less common with reports of reactions to propofol, thiopentone and etomidate [24–26]. Other causes such as NSAIDs, other analgesics, colloids, chlorhexidine and diagnostic agents, which were not recorded by these studies, are increasingly seen [27] (Fig. 2). There are case reports of anaphylaxis to fentanyl [28] and neostigmine [29]. Allergy to LAs remains rare. There are no reported cases of allergy to inhaled anaesthetics.

**Table 3.** Changing aetiological patterns of anaphylaxis during anaesthesia from 1990 to 2002 in France

Cause (%)	1990–1991 (n = 1585) [3]	1999–2000 (n = 789) [5]	2001–2002 (n = 712) [6]
Anaphylaxis	52	66	69
Anaphylactoid (no identified cause)	48	34	31
% of anaphylaxis due to			
NMBAs	70	58.2	55
Latex	12.6	16.7	22.3
Antibiotics	2.6	15.1	14.7
Others	14.8	10	8
% Overall due to	36	38	38
NMBAs			
% Overall other than	64	62	62
NMBAs			
Commonest NMBA (%)	Sux 43%	Roc 43%	Sux 37%
of NMBA group)	Vec 37%	Sux 23%	Roc 26%

NMBA, neuromuscular blocking agent; Roc, rocuronium; Sux, suxamethonium; Vec, vecuronium; n, number of patients.

#### *Anaesthetic drugs given at induction (neuromuscular blocking agents, intravenous anaesthetics and opiates)*

The anaesthetic drugs given at induction are shown in text box 3. Within the NMBAs, suxamethonium was previously the most common cause of anaphylaxis (43% of all NMBA reactions in France 1990–1991 [3]), but the changing pattern of drug use has led to an increase in cases due to other agents, particularly atracurium, rocuronium and cisatracurium. A high incidence of allergy to rocuronium in the 2001 French series and other studies has been reported (26% of NMBAs) [5, 6, 30–32]. It was suggested that the lower incidence of cisatracurium allergy may have been an underestimate, because positive skin tests were mistakenly assumed to be due to non-specific histamine release [33]. However, current standardized protocols for skin testing with cisatracurium should allow the incidence to be established. Of the NMBAs, allergy to pancuronium and gallamine (no longer available in the United Kingdom) appears rare [34, 35].

Opiates may be administered at a number of points before, during and post-operatively. Therefore, although allergic reactions to morphine, pethidine, codeine and papaveretum (no longer available) are uncommon [36], these can occur at any time (Table 2). Non-immune mediator release is common after morphine and pethidine [36] but uncommon after fentanyl or remifentanyl ([37]; and unpublished data).

#### *Skin prick tests*

The purpose of skin prick tests (SPTs) is to demonstrate specific IgE antibodies. Experience in SPT is particularly important in drug allergy due to the lack of validated tests

**box 3.** Main groups of general anaesthetic drugs which may cause anaphylactic reactions

(A) Intravenous anaesthetics	thiopental, propofol, etomidate, ketamine, midazolam
(B) Opioid anaesthetics	fentanyl, alfentanil, remifentanyl, morphine, pethidine
(C) Neuromuscular blockers (muscle relaxants, NMBAs)	(i) Non-depolarizing atracurium, cisatracurium, mivacurium, rocuronium, vecuronium, pancuronium, (ii) Depolarizing Suxamethonium

for most drugs and difficulties with interpretation. Drugs used for induction of anaesthesia that are suspected to have caused anaphylaxis cannot be re-administered; hence, positive skin tests can never be fully validated. Some drugs (e.g. some opiates, atracurium, mivacurium) have direct histamine-releasing activity and therefore may cause flushing immediately on administration and result in false-positive weals on skin testing normal subjects. With opiates skin tests do not distinguish a subject suffering an anaphylactic reaction from a normal control subject because both are likely to have positive results [36]. There is no absolute consensus on the concentration of NMBAs and i.v. anaesthetics to be used for skin testing. More data in control subjects are required.

The aim of skin testing should be (i) to identify the cause and (ii) to identify other anaesthetic agents likely to be safe for future use. It is therefore essential to test a range of drugs, including several from each group in text box 3, as well as all of the drugs given. Muscle relaxants remain the most common single cause [6, 8] and, because there can be cross-sensitivity between NMBAs, all drugs in this class should be tested if NMBA allergy is suspected. There is no reason to delay skin testing after the allergic reaction, and this can be considered as soon as the patient has recovered from the reaction and the effects of the drugs used to treat anaphylaxis.

The UK recommendation is that SPT to anaesthetic agents should be at two concentrations: 'neat' (i.e. stock solution as used clinically) and at a 1/10 dilution simultaneously (Table 4). The 1/10 dilution is used to reduce false-positives from drugs with intrinsic histamine-releasing activity. Weals resulting from anaesthetic agents are commonly smaller than those resulting from other allergens causing anaphylaxis and rarely > 6 mm diameter making interpretation difficult. To be certain of a positive, a weal diameter of at least 2 mm greater than the negative control should be seen at a 1/10 dilution. A positive weal to neat, but negative to 1/10, may be considered diagnostic in some circumstances if the drug fits the clinical picture and other possible drugs are ruled out. The NMBAs most likely to cause non-specific weals are atracurium,



**Table 4.** Concentrations for skin testing for neuromuscular blocking agents (NMBAs) and intravenous (i.v.) anaesthetics

Drug	Undiluted concentration 'neat'	SPT test concentration	IDT test concentration (dilution of neat)*	Histamine releasing propensity
	(mg/mL)			
Atracurium	10	Undiluted and 1/10	1/1000	+
Cisatracurium	2	Undiluted and 1/10	1/100	
Mivacurium	2	Undiluted and 1/10	1/200	+
Rocuronium	10	Undiluted and 1/10	1/200	+
Pancuronium	2	Undiluted and 1/10	1/10	
Vecuronium	2	Undiluted and 1/10	1/10	
Suxamethonium	50	Undiluted and 1/10	1/500	+
Etomidate	2	Undiluted and 1/10	1/10	
Ketamine	10	Undiluted and 1/10	1/10	
Propofol	10	Undiluted and 1/10	1/10	
Thiopental	25	Undiluted and 1/10	1/10	

\*Testing at higher concentrations may be undertaken if drug strongly and initial testing negative.

SPT, skin prick test; IDT, intradermal test.

Adapted from Mertes et al. [38, 56].

mivacurium and rocuronium: some authors recommend SPT to these at a 1/10 dilution only [38–40] although UK practice is to test these drugs at 'neat' and 1/10 dilution.

Positive (histamine) and negative (saline) controls must always be included. There is lack of data on shelf-life of diluted NMBAs and i.v. anaesthetics and this, compounded by the difficulty in validating tests, makes recommendations difficult. Therefore, a new drug vial should always be used whenever a skin test result is obtained that is inconsistent with the clinical picture. The French have recommended that drug dilutions can be stored for up to 3 months at 4 °C, except for atracurium, rocuronium, mivacurium and cisatracurium, which should be freshly diluted [41].

**Validation of skin prick tests.** There are considerable data on the value of skin testing for NMBAs [42–45] but it is not possible to validate positive skin tests to NMBAs or i.v. anaesthetics using the gold standard of incremental drug challenge. However, there are reports of deaths after a drug identified by positive skin test was re-administered [46]. Therefore, the sensitivity of a positive skin test to i.v. anaesthetics and NMBAs remains unknown and validation is based on correlation of a positive SPT with the clinical picture and restricted to drugs for which there are extensive data. When assessed against the allergist's clinical diagnosis, the positive and negative 'predictive values' appear good but unvalidated. A study of several drugs including antibiotics, NMBAs and other drugs used during anaesthesia showed good positive and negative predictive values for SPT for suspected drug allergy [47]. This contrasts with a Danish series of 67 cases in which an

informed guess by the anaesthetist or surgeon was unreliable and in only 7% of cases matched the results from subsequent allergy testing [48].

Positive skin tests to NMBAs not administered at the time of the reaction are identified when skin testing is carried out to a wide range of drugs. The significance of these is not known, but they should be identified as a potential risk and avoidance recommended in order to avoid allergic reactions due to cross-reactivity. One should be particularly wary of false-negative results as there are case reports of anaphylaxis after a negative skin test [49]. If no cause can be identified, one cannot be certain if this was due to a false-negative skin test, which may re-expose the patient to the same or a related NMBA [49, 50].

### Screening

Screening subjects without a prior history of allergic drug reactions is not recommended because there is a discrepancy between SPT results and clinical outcomes [51]. One study screening anaesthesia-naïve subjects reported that 9.3% had either a positive skin test to one or more NMBAs or the presence of specific IgE to quaternary ammonium ions [52].

### Intradermal tests

Intradermal tests (IDTs) should be undertaken if SPTs are negative for a drug suspected to be the cause, and the mechanism of reaction to that drug is such that intradermal testing is appropriate. IDTs may also be used to exclude cross-sensitivity of NMBAs when the cause has been identified from intradermal testing, but the specificity of such testing is not known. There are difficulties in interpretation because intrinsic histamine releasing activity is more marked on IDT, increasing the potential for false-positive results and reducing the specificity of the test. Interpretation is even more difficult if higher concentrations of the drug are used for intradermal testing with a greater likelihood of false-positive results.

There is no consensus on skin testing methods. Most opinion comes from a few groups with some recommending SPT, others IDT [5, 53], and yet others suggest both methods are valid and it is optional which to use [38, 54]. Studies have reported similar diagnostic value and up to 97% concordance between intradermal testing vs. SPT for NMBAs [4, 45, 55]. In a study of suxamethonium allergic patients, those with the strongest positive SPTs (one-third of all with positive SPT), IDTs were positive in 13 of 15 (tested at 1/1000), which may reflect inadequate technique in the two patients with negative results [46].

**Technical aspects.** Drugs should be diluted for skin testing, although there is a lack of evidence-based consensus

(Table 4). NMBAs, particularly atracurium but also mivacurium and rocuronium, may result in false-positive intradermal reactions in normal subjects at 1/100 of therapeutic concentrations; therefore, lower initial concentrations may be necessary [38–40]. A further study to determine the minimum dilution for IDT proposed that rocuronium and mivacurium could be used at 1/200 (instead of the previous recommendation of 1/100 and 1/1000, respectively) [56]. In this study, none of the normal subjects had a positive reaction at 1/164 dilution. In the United Kingdom, the practice is to conduct IDTs to NMBAs at the highest concentration that does not cause a reaction in normal subjects. In France, the practice is to start at very low concentrations and then to continue at 10-fold increments. For colloids, there are no published series, and so experience is critical. A negative SPT is often found and intradermal testing required at concentrations ranging from 1/100 dilution to the therapeutic concentration. A bleb of 4–6 mm should be produced by injecting about 0.03 mL. By convention, a positive IDT is defined as a weal that is at least 3 mm larger than the initial bleb and has a flare. A negative control with saline is essential. However, with NMBAs there is a lack of consensus on what constitutes a positive result and experience suggests that a persistent weal at 20–30 min, without enlargement, plus a flare and itch may be positive. In a negative test, the weal usually becomes flat and in this situation a higher concentration may be considered if the drug is suspected.

For most drugs other than NMBAs but including anti-

biotics and colloids, IDTs are more likely to be positive than SPTs. However, there is a lack of published data to help with interpretation and these tests should therefore be focused in centres with extensive experience from large numbers of patients. In patients with a suspected allergy to NMBAs, IDTs are only required if SPTs are negative or to distinguish cross-reacting drugs if an IDT was necessary to identify the causative agent.

When it is clinically likely that an agent given at induction has caused an allergic reaction, but the cause has not been identified on the initial visit, the skin tests should be repeated at a later date.

**Cross-reactivity of NMBAs.** Cross-sensitization occurs commonly among NMBAs (Table 5). This can be detected by SPT, but much higher rates (60–84%) are found by intradermal testing, although only a minority react to all drugs tested [38, 42, 46, 49, 55]. An even higher rate of 97% was found in 31 patients using a combination of five tests [57]. In this study, rocuronium was the least cross-reactive, with one-third of those sensitive to NMBAs not reacting. The concentration used for testing is important to avoid non-specific positives especially with atracurium. SPT is sufficient to detect cross-reacting drugs if there is a positive SPT to the index drug. However, if the index drug is only detected by IDT, then it is usually necessary to undertake IDTs to other NMBs to exclude cross-sensitization. Cross-sensitization is commonly found within groups, e.g. the benzyliisoquinoliniums, but

Table 5. Cross-sensitivity for neuromuscular blocking drugs

Source reference	Design and sample	Drug	Intervention or test	Cross-sensitivity
Fisher Baldo [7]	XR NMBAs Review	NMBAs	SPT or IDT or QA-RIA	In up to 60% Greatest with QA-RIA
Fisher and Munro [109]	XR NMBAs 67 patients GR to a NMBA	NMBAs Sux Alc Gall Pan Tubo Deca	IDT Comparison of pairs of drug	Widely variable depending on pair tested Most low Sux/gall XR high, in 36%
Laxenaire <i>et al.</i> [57]	XR Roc with other NMBAs 31 patients GR to a NMBA 10 controls SPT Roc	NMBAs Roc Sux Gall Vec Pan Atra	SPT Neat (Atra ND) IDT ( $10^{-4}$ to $10^{-1}$ serial dilutions) RAST (QA-RIA) LHR	In 97% (30/31 – which drug/s varied) on ID (1 patient with no XR was sensitive to Gall, but other Gall-sensitive patients showed XR) Roc least X-reactive 1/3rd sensitized to NMBA not sensitized to Roc $10^{-1}$ Roc no intrinsic histamine release activity

Roc, rocuronium; Sux, suxamethonium; Gall\*, gallamine; Vec, vecuronium; Pan, pancuronium; Atra, atracurium; Tubo, tubocurarine; Dec\*, decamethonium; Alc\*, alcuronium; XR, cross-reactivity; ND, not done; QA-RIA, quaternary ammonium radioimmunoassay; LHR, leucocyte histamine release; GR, generalized reaction.

\*No longer available in the United Kingdom.

can occur between groups. Although the clinical significance of cross-reacting skin tests to NMBAs is not known, we recommend that any NMBAs giving rise to a positive skin test should be avoided as it would be impractical to undertake provocation testing.

**Intrinsic histamine releasing activity.** One of the difficulties with interpretation of skin tests is to distinguish 'false positives' due to intrinsic histamine-releasing activity, from positives due to specific IgE antibody. This is more of a problem with IDT than SPT. *In vitro* studies showed that suxamethonium, vecuronium and atracurium did not induce histamine release from human basophils. Findings vary with skin or lung mast cells, but atracurium induced a concentration-dependent histamine release from both cell types [58]. This is in keeping with the observation that atracurium may result in small non-specific weals on skin testing.

Atracurium and mivacurium (and gallamine) are known to have histamine-releasing activity. Administration of atracurium in fit, non-allergic patients was associated with a 234% increase in plasma histamine and a fall in mean arterial pressure of 22%. The corresponding figures for rocuronium were 20% and 4.3% [59]. Hosking et al. [60] demonstrated that atracurium-induced hypotension can be minimized by pre-administration of an H1 blocking drug.

**Safety.** Although systemic reactions have been reported, generally SPTs to these drugs even in patients with anaphylaxis appear to be safe [55]. IDTs are associated with a higher risk of systemic reactions. The investigating doctor must carefully tailor the investigation to each patient to optimize diagnostic yield while considering the risks involved. All skin testing should be carried out in a specialist allergy setting, by staff trained to treat anaphylaxis and the appropriate drugs, including adrenaline immediately available.

#### *Serum-specific IgE antibodies*

Tests for serum-specific IgE antibodies [radioallergosorbent test (RAST) or ImmunoCAP<sup>TM</sup>, Phadia AB, Uppsala, Sweden] to suxamethonium, gelatine, certain antibiotics, latex and chlorhexidine are commercially available. Published data and clinical practice suggest that there is often only partial correlation between the suxamethonium-specific IgE and SPT [61, 62]. However, sometimes additional information may be derived from measurement of specific serum IgE antibodies, particularly when SPT is inconclusive. Skin tests are also preferable because a wide range of drugs can be tested and results are immediately available allowing further steps in testing. A recently introduced assay for quaternary ammonium/morphine (ImmunoCAP<sup>®</sup> Allergen c260) may prove useful with

further validation when the results from skin testing are equivocal although the specificity is affected by high total IgE levels [63, 64].

#### *Experimental tests*

Tests for basophil activation using flow-cytometry after incubation with specific drugs are used in research settings. Their usefulness is still being evaluated and they are not currently recommended for routine clinical practice.

#### *Other causes*

Latex, antibiotic and NSAID sensitivity are included but not covered in depth here. Their detailed investigations will be outlined in separate guidelines. This guideline focuses on issues specific to the anaesthetic setting.

#### *Latex allergy*

Latex allergy is an important cause of anaphylaxis during anaesthesia (Table 3) [5, 65, 66]. However, experience from major allergy centres indicates that it is less common in the United Kingdom. Systemic reactions to latex rubber are IgE-mediated. It is important to distinguish this from contact dermatitis to chemicals used in the manufacture of rubber, which is a different disorder with different implications and requiring less stringent avoidance during surgery. Contact dermatitis causes slow-onset eczematous reactions, is not life threatening and caused by a type IV reaction and thus IgE antibodies are not involved.

Latex allergy is common, with a prevalence of 1.4% in the general population but with sensitization rates of up to 7% [67, 68]. It is most common in atopic subjects, females and populations exposed frequently, e.g. health care workers (allergy in up to 3% but sensitization in up to 16%) [69–74], domestics, laboratory workers and in patients undergoing repeated surgery or procedures with exposure to rubber products, e.g. women treated with IVF or children with meningomyeloceles and spina bifida [75, 76] or surgery in the first year of life [77]. Since the introduction of non-powdered latex gloves in UK hospitals, there appears to be a considerable reduction in development of latex allergy in health care workers.

Allergic reactions to latex occur intra-operatively as time is needed to absorb the allergen through the mucosa or peritoneum. A systemic reaction is unlikely to occur within a few minutes of latex exposure. If latex allergy is suspected, SPTs and serum-specific IgE tests should be undertaken. SPTs are superior to serum assays [78, 79], with a greater sensitivity and specificity than specific IgE. If there is doubt after one of the commercial solutions has been used, a direct skin prick through a latex surgical glove may give a positive result. A variety of assays for serum-specific latex IgE are available. In a study

comparing three different methods for serum latex IgE to SPT, the best latex IgE detection system (Immulate<sup>®</sup>, Immulite instruments, Siemens Healthcare Diagnostics, Flanders, NJ, USA) misclassified as negative over 15% of skin test-positive individuals [80]. These results support the value of SPTs. Another study comparing different assay systems in volunteer health care workers found a wide between-assay variation in positive specific IgE results (3.6–43.6% for serum assays and 2.9–14.3% for different skin test reagents). No correlation was found between self-reported but unconfirmed symptoms of type I allergy and any test method [81]. A clinical history is essential and test results should not be interpreted in isolation. If latex allergy is strongly suspected and skin test and serum-specific IgE is negative, glove challenge (exposing the patient to latex by wearing a latex glove for increasing periods while monitoring for objective signs of an allergic reaction) should be undertaken. If glove challenge is negative, a buccal challenge should be undertaken.

*Interpretation of latex skin tests and radioallergosorbent tests.* In the investigation of latex allergy, a common misunderstanding is to assume that the presence of specific IgE to latex indicates clinical allergy. For common inhaled allergens, at least 40% of the population are atopic, yet only about one-third of these develop expression of this sensitization (clinical allergy) [82, 83]. The equivalent figures are not certain for latex allergy, but appear to follow the same general pattern. Many published studies on latex allergy (especially in health care workers) report on sensitization to latex rubber (the presence of latex IgE) and this varies from 3% to 16% in different series [69–73]. The incidence of clinical allergy is often not reported, but some papers distinguish the two. In a large study, almost 60% of those with positive skin tests to latex had symptoms [70]. In another study, 6.8% had positive skin tests and 3.3% had symptoms of latex allergy [71]. Therefore, without a detailed clinical history, a positive latex-specific IgE result in isolation can be misleading. Recombinant allergens used for detecting specific IgE may play a role once further clinical correlation has been undertaken. For example, positive skin tests to the recombinant latex allergens Hev b 5, 6 and 7 had a sensitivity of 93% in a group of latex allergy subjects [84].

*Sources of exposure and avoidance.* Thin stretchy rubber products are most likely to induce an allergic reaction, particularly surgical gloves, balloons and condoms [65]. Solid black rubber is inert and less likely to cause symptoms. Many products are no longer made of rubber, e.g. most urinary catheters, face masks and endotracheal tubes are now non-latex. Theatres must have the facility to provide a latex-free environment for latex-allergic patients and must therefore have a list and supply of

latex-free products [78]. Trust latex policies provide information on this. The introduction of non-powdered latex gloves has substantially reduced the incidence of latex sensitization in health care workers [85].

### *Antibiotics including penicillin*

I.v. antibiotics are often given at induction, commonly within a minute of induction agents, and consequently a reaction would occur early (Table 2). If skin testing excludes the induction agents and NMBA, other drugs such as antibiotics given at the same time become a likely cause.

There is extensive literature on the value of tests for  $\beta$ -lactam/penicillin allergy, but less is known about tests for other antibiotics. Reactions to penicillin may result from a variety of mechanisms, for example maculopapular rashes are not IgE-mediated, but severe, immediate reactions and particularly anaphylaxis are usually IgE-mediated [86]. For skin testing, a minor determinant mix and separately benzyl-penicillin should be tested, in addition to the major determinant penicilloyl polylysine, amoxicillin and the suspected  $\beta$ -lactam. A positive skin test is helpful to corroborate a clear history [87–89]. A negative skin test result is also helpful but its usefulness varies depending on which  $\beta$ -lactam is tested. In the majority of cases if anaphylaxis has occurred, a skin test is likely to confirm or refute penicillin allergy. A positive skin test has less predictive value when the history is less clear. For similar reasons interpretation of results of serum-specific IgE antibodies to penicillin G and V (RAST) is also not straightforward and depends on the clinical picture. IDT should be carried out in patients with negative or equivocal SPT results (Fig. 3). The gold standard is a provocation test but should only be considered if skin tests are negative. Less commonly, patients are shown to be allergic by challenge despite negative SPT and IDT; this is more unusual if the reaction was anaphylaxis. If challenge is required this should preferably be undertaken with the oral version or a closely related oral preparation if the suspected cause is only available as an i.v. preparation. I.v. or intramuscular challenge should be avoided if possible, but may be required infrequently.

If a cephalosporin is suspected to be the cause, the process is to test the index cephalosporin and penicillin allergy determinants and, if both are negative, challenge with cephalosporin is undertaken. For non- $\beta$ -lactam antibiotics, there are less data on sensitivity and specificity of tests and the approach is by sequential testing: SPT – if negative: IDT – if negative: oral challenge considered.

### *Colloids*

Reactions may occur rarely to gelatin containing colloids, such as Gelofusine<sup>™</sup> (B Braun Medical, Sheffield, UK), Haemaccel<sup>™</sup> (Aventis Pharma Ltd., West Malling, UK) or

Volplex™ (Maelor plc, Wrexham, UK). These are more difficult to diagnose clinically, partly because of the delayed and variable onset from the start of the i.v. infusion, although this is usually within 30 min. A further problem is that the mechanism, and hence the appropriate test, has not been established. A small number of patients have been studied in specialist centres and SPTs to Gelofusine™ (gelatin) are often negative but IDTs positive. One study of six patients found the *in vitro* basophil activation test positive, with a sensitivity of 100% and high specificity [90]. In terms of acute management it should be noted that the correction of hypotension with bolus infusions will paradoxically sustain the allergic reaction if the fluid used is indeed the trigger [91]. In one fatal reaction during anaesthesia, attributed to Haemacel™, investigation suggested this was a kinin-mediated anaphylactoid reaction [92]. Reactions to colloids present with sudden loss of blood pressure, compatible with widespread vasodilation and generation of bradykinin is a possible mechanism [91]. Limited data show positive ID tests with negative SPTs, which could occur as a result of generation of kinins. It is not known if these reactions are IgE-mediated but the SPT can be positive. There is lack of data in normal subjects and as these tests have not been validated they should only be interpreted in the light of the clinical picture.

### Dextrans

Anaphylactoid reactions to dextrans, e.g. Dextran 40 and Dextran 70, are described but are even less commonly seen than reactions to gelatine [93, 94]. These are due to dextran-reactive IgG antibodies.

### Non-steroidal anti-inflammatory drugs

NSAIDs, including aspirin, can cause reactions, by inhibition of cyclo-oxygenase, resulting in generation of leukotrienes [95, 96]. NSAIDs are increasingly recognized as a cause of non-IgE-mediated anaphylactic reactions. They may be given rectally towards the end of surgery, i.v., or sometimes with pre-medication, depending on the procedure. The onset of reaction is usually up to 10 min after i.v. administration, 15–30 min from rectal administration and 30–60 min after oral administration. If the onset of reaction is at the end of surgery, this immediately excludes the induction agents, and the main differential diagnosis is an NSAID given rectally late during the procedure, latex allergy or a reaction to colloid. There are no reliable diagnostic tests for NSAID intolerance and this is essentially a clinical diagnosis, having excluded other potential causes (such as NMBAs and latex rubber). However, the diagnosis can be confirmed by provocation, but this should only be considered if there is doubt from the history [97].

### Syntocinon

Anaphylactoid reactions to syntocinon have been reported but this is extremely rare [98, 99].

### Reversal agents

This is very rare. There is a single case report of anaphylaxis to neostigmine [29], and one case listed in a large series of 826 patients but no data given [8].

### Antiseptics

Reactions occur after instillation of chlorhexidine to the bladder after surgery, but also to skin painting and during central venous catheter insertion. A cluster of cases was reported from Denmark [27]. Positive SPTs and serum-specific IgE are found in a significant proportion of patients, but not universally [100–103]. If the clinical history is indicative with a negative skin test, challenge should be considered by applying the solution to the skin, in incremental amounts. Anaphylaxis also occurs to povidone iodine although this appears to be less common.

### Patent Blue V

Anaphylaxis is seen increasingly since the introduction of Patent Blue V injection and reported in 1.1% of patients with breast carcinoma undergoing surgery with sentinel lymphadenectomy [104]. However, only a few cases are reported where allergy testing has been undertaken. The reaction occurs about 10–30 min after administration of the dye, and is often severe with symptoms lasting for several hours [105, 106]. SPTs are sometimes positive to the neat solution but, if negative, IDTs at 1/100 dilution should be undertaken. There are no data on positive and negative predictive values.

### Local anaesthetic allergy

This is rare. During general anaesthesia, an LA may be administered in a spinal anaesthetic or given i.v. with propofol. Because of the rarity of proven LA allergy, it has not been possible to validate SPT and IDT [107, 108] but there is no evidence that these tests are useful. Therefore, after SPT, IDT is undertaken for safety reasons, and it is then essential to proceed to incremental subcutaneous challenge.

### Reporting of results

This is a critical part of the process. A number of actions are required (box 2 and Fig. 2). A letter should be provided identifying the cause and any cross-reacting drugs. In addition, a list of NMBAs to which skin tests are negative

should be provided to identify anaesthetic drugs likely to be safe for future anaesthetics. When no cause can be identified, caution should be advised with future general anaesthetics, the previously administered suspect drugs and any cross-reacting drugs to which the skin test was positive must be avoided.

#### Future research and audit

1. Extensive epidemiological studies in the United Kingdom on the incidence of allergic reactions during general anaesthesia.
2. Audits describing how often these reactions reach an allergist and the outcome of the investigations.
3. Studies investigating a breakdown of the aetiology in the United Kingdom.
4. Studies investigating and validating *in vitro* assays in both IgE- and non-IgE-induced reactions.

#### Acknowledgements

The preparation of this document has benefited from extensive discussions within the Standards of Care Committee of the BSACI and we would like to acknowledge members of this committee for their valuable contribution namely Andrew Clark, Sophie Farooque, Steven Jolles, Susan Leech, Ian Pollock, Richard Powell, Glenis Scadding, Nasir Siddique and Samantha Walker. We would also like to acknowledge the very valuable considerations and helpful suggestions we received from many BSACI members during the consultation process. Also, special thanks go to Dr Pia Huber for her valuable help in editing and incorporating critiques provided by the members of SOCC.

These *guidelines* inform the management of suspected anaphylaxis during general anaesthesia. Adherence to these guidelines does not constitute an automatic defence for negligence and conversely non-adherence is not indicative of negligence. It is anticipated that these guidelines will be reviewed 5 yearly.

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